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EDITORIAL COMMENT

Echocardiography Contrast for Image Optimization: Beyond Confidence, It Is a Matter of Accuracy*

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Since the first intravenously administered echocardiographic contrast agent capable of left ventricular cavity opacification to enhance visualization of the endocardium was approved by the Food and Drug Administration (FDA) more than 13 years ago, important advances in these agents and in the ultrasound equipment permitting their detection have occurred.

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Current agents not only scatter and reflect, but also interact with administered ultrasound through harmonic and multipulse sequencing to increase signal intensity over background tissue noise. Modifications in the agents, along with these unique methods of ultrasound delivery and reception, have resulted in robust and persistent contrast effect. There has been wide clinical acceptance of contrast agents for the application of improving echocardiographic imaging in patients for whom initial transthoracic images are technically suboptimal. Administration of these agents in a busy clinical practice has been shown to be efficient and cost-effective (1).

Accurate visualization of endocardial borders is of crucial importance in stress echocardiography, as this technique involves assessment of global and segmental wall thickening and motion (2). In this test, the endocardial border must be assessed quickly and in multiple planes. Not surprisingly, this has become the area of echocardiography in which contrast agents are most frequently used.

In this issue of *JACC: Cardiovascular Imaging*, Plana et al. (3) report new evidence that contrast agents increased the accuracy of dobutamine stress echocardiography for detection of angiographic coronary artery disease. In this prospective study, 101 patients underwent, in randomized order, 2 dobutamine stress tests performed at least 4 h but no more than 24 h apart, 1 with and 1 without a contrast agent. Harmonic imaging was used for all studies, and ultrasound settings were optimized for endocardial border detection. Echocardiograms were reviewed by a single observer who was blinded to other data. In the 92 patients who underwent coronary angiography, accurate detection of ischemia, represented as new or worsening regional wall motion abnormality, corresponding to angiographic stenosis ≥70% narrowing of the lumen diameter was significantly higher with contrast agents than without. Not surprisingly, the impact of contrast agents on accuracy was greatest in studies in which confidence of interpretation of regional wall motion was low without contrast agents. In this subgroup, accuracy increased from 36% to 68% ($p = 0.01$).

Plana et al. (3) found that contrast agents increased endocardial visualization at rest and during stress and increased the confidence of interpretation of the studies. This confirms the previous observations of Rainbird et al. (4), in which 300 consecutive patients underwent contrast dobutamine stress echocardiography; images were interpreted with and without the use of intravenous contrast agents. In this study, the percentage of wall segments visualized at rest increased from 96.4 ± 9.6% to 99.7 ± 2.5% ($p < 0.01$) with the addition of contrast agents and at peak stress from 94.4 ± 13.7% to 99.8 ± 1.5% ($p < 0.01$). Similarly, the confidence of interpretation was superior with contrast imaging compared with noncontrast imaging both at rest ($p < 0.01$) and at peak stress ($p < 0.01$).

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Although the confidence of interpretation declined in the comparison of rest to peak stress images, this did not occur when contrast agents were administered. Although all image quality subgroups benefited from the use of contrast agents, those with the poorest quality images benefited the most (4).

Why Has It Taken So Long to Demonstrate That Contrast Agents Improve Accuracy of Stress Echocardiography?

First, the effect of contrast agents on accuracy could not be demonstrated without referral of sufficient numbers of patients for coronary angiography. Second, it was also necessary that a sufficient number of noncontrast agent studies be of suboptimal quality; it is in this situation that contrast agents provide the greatest benefit. In the study by Rainbird et al. (4), in which noncontrast image quality was generally good, only 35 patients underwent coronary angiography. In this small subgroup, no benefit of contrast agents on the accuracy of stress echocardiography could be demonstrated. The current study was logistically challenging, as 2 dobutamine stress echocardiograms, with and without a contrast agent, were performed in each patient. Furthermore, 91% of patients underwent coronary angiography. The investigators are to be congratulated on undertaking and completing this ambitious study.

In Which Patients Undergoing Stress Echocardiography Should Contrast Agents for LV Cavity Opacification Be Used?

The American Society of Echocardiography recommends that contrast agents be used when 2 or more endocardial segments cannot be adequately visualized (2). These guidelines are reasonable and appropriate. In the current study, the accuracy for detection of ischemia was significantly higher only for circumflex lesions ($p = 0.0009$), probably because of technical difficulties in visualizing the lateral wall and the smaller amount of myocardium subtended by this vessel. Importantly, there was no impact attributed to contrast agents in studies interpreted with high confidence. Contrast agents increase the expense of performing a stress echocardiogram and are not necessary in the majority of patients, that is, those in whom assessment of regional wall motion is feasible without contrast agents.

Are Contrast Agents Safe?

The FDA has recently issued a black box warning about the safety of echocardiography contrast agents. This warning was issued on the basis of post-marketing reports of deaths that were temporally related to contrast agent use in 4 patients with significant underlying progressive cardiovascular disease and approximately 190 other variably characterized nonfatal adverse events, without conclusive evidence of causality. These events occurred over a 6-year period during which approximately 2 million patient doses of contrast agents were administered, for a mortality rate of approximately 1 in 500,000. Indeed, most large echocardiography laboratories have used these agents in hundreds or thousands of patients, especially for stress echocardiography, without any fatalities. Occasional intolerance and rare allergic reactions (estimated rate 1 in 10,000) have been noted. Because stress echocardiography involves the study of patients who are in sufficiently stable condition to withstand stress testing and because monitoring of the electrocardiogram and vital signs is a standard part of the test, contrast agents for endocardial border detection can continue to be safely performed in these patients; that is the practice at the Mayo Clinic. We continue to use a sonographer-driven decision-making algorithm for contrast agent use with screening for safety performed by our trained registered nurses, who are cognizant of the new contraindications in the revised package insert, and continue to obtain verbal consent from the patient before administration.

Current interest in echocardiography contrast technique has focused on myocardial perfusion and combinations of perfusion images with regional wall motion assessment during stress echocardiography, as can be achieved with off-label use of existing contrast agents. Ultrasound settings for appreciating myocardial contrast involve the use of a combination of high and low mechanical index settings. Investigators have shown that inducible perfusion abnormalities seen with myocardial contrast echocardiography may occur before regional wall motion abnormalities and that myocardial perfusion imaging during dobutamine stress echocardiography provides incremental prognostic information in patients with known or suspected coronary artery disease (5,6). In fact, initial findings have suggested that quantitative assessment of the systolic to diastolic ratio of arteriolar blood volume might be used to detect coronary stenosis without the need for a stress test (7). However, although

unique agents are currently undergoing the rigors of FDA evaluation, there is not yet an approved echo contrast agent for myocardial perfusion imaging.

In conclusion, contrast agent use during stress echocardiography has been clearly demonstrated to improve visualization of endocardial border segments and confidence of test interpretation in patients for whom noncontrast images are suboptimal. Plana et al. (3) have confirmed the logical extension of this observation: if you can better see the structures required for interpretation of the study results, test performance will be more accurate. Ultrasound imaging technology now permits simultaneous detection of left ventricular cavity opacification and myocardial perfusion. Further studies in large numbers of patients are needed to establish the incremental role of contrast agents, when combined with perfusion assessments, for evaluating the patient with known or suspected coronary artery disease.

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